REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 30-58 are in this case. Claims 30-58 have been rejected. Claims 30, 32, 34, 38, 40, 45, 52-55, and 57-58 have now been amended. New claim 64 has now been added.

Information Disclosure Statement

The Examiner states that the listing of references in the specification is not a proper information disclosure statement and unless they have been recited by the Examiner on the form PTO-892, they have not been considered. Please find enclosed an information disclosure statement listing the references cited in the specification.

Abstract

The Examiner states that the abstract is too short and does not fully describe the claimed invention. Please find included a revised abstract replacing the abstract filed with the application and which describes the claimed invention.

35 U.S.C. § 112, First Paragraph, Rejections

The Examiner has rejected claims 30-58 under 35 U.S.C. § 112, first paragraph, because the specification while being enabling for the limited number of complex carbohydrate libraries disclosed, does not reasonably provide enablement for any complex carbohydrate library which claim 30 literally encompasses. The Examiner's rejections are respectfully traversed. Claims 30, 32, 34, 38, 40, 45, 52-55, and 57-58 have now been amended.

The Examiner states that claim 30 encompasses complex carbohydrate libraries with carbohydrate members that are unbound by the number of saccharide units etc. and carbohydrate members that have yet to be prepared or envisioned.

The present invention relates to methods of synthesizing a complex carbohydrate library which is attached in an addressable manner to a single solid support (e.g., an array) and is thus highly suitable for various screening assays.

As is clearly illustrated in the instant application, the present inventors have developed a novel enzymatic synthesis approach which enables parallel synthesis of a plurality of distinct complex carbohydrates directly on an addressable support.

The synthesis methodology outlined in the instant application was developed for the sole purpose of constructing the libraries of the present invention. Numerous parameters were considered while reducing the present methodology to practice:

(a) The availability of glycosyltransferase enzymes.

(b) What are the enzymes that have to be employed for each enzymatic step and at what sequence?

(c) The architecture and surface chemistry of the solid phase substrate used for the synthesis. Especially from the following considerations:

(i) how to monitor the multiple enzymatic synthesis reactions on a micro array and how to monitor multiple steps per each site on the array; and

(ii) how to prevent the enzymes used for synthesis from adsorbing non specifically to the surface and thus contaminating the surface of the support.

The instant application provides examples of parameters for synthesizing a few select structures in efforts of demonstrating the novel and efficient synthesis methodology developed by the present inventors. It will be appreciated that it is impossible to describe the parameters underlying the synthesis of all possible complex carbohydrate structures since, for all intents and purposes, that represents an infinite number of structures.

Thus, it is Applicant's strong opinion that the assertion of the Examiner that the specification teaches a limited number of complex carbohydrate libraries

and as such, it does not reasonably provide enablement for any complex carbohydrate library which claim 30 literally encompasses is erroneous.

One of the requirements of the *in-situ* enzymatic synthesis method of the present invention is a diverse repertoire of glycosyltransferases. Although at the time of priority of the instant application only a few types of glycosyltransferases were routinely used (commercially available glycosyl transferases were mainly limited to β 1,4 Galactosyltransferase, α 2,3 and α 2,6 sialyltransferase and α 1,3/4 fucosyltransferase) DNA sequences of a diverse group of glycosyltransferases were available at the time and as such, using molecular and biochemical techniques, one of ordinary skill in the art would be capable of generating a large repertoire of glycosyltransferases. It should be noted that the lack of enzyme availability indicates the general lack of interest in enzymatic synthesis of complex carbohydrates further emphasizing the novelty of the present invention.

By providing the enzyme sets and enzymatic reaction steps necessary for generating relatively small complex carbohydrate structures which are in essence the building blocks of large complex carbohydrates, the present inventors provide the skilled artisan with the tools necessary to synthesize <u>any</u> complex carbohydrate structure since in essence, large complex carbohydrate structures are synthesized using the same synthesis considerations used for generating relatively small carbohydrate structures.

In addition to teaching the ordinary skilled artisan how to acquire and utilize a specific enzyme set for the synthesis of a particular complex carbohydrate structure, the instant application also teaches the skilled artisan how to select and utilize enzyme sets which are not specifically described in the specification. Thus, the instant application also teaches the ordinary skilled artisan how to apply the teachings of the present invention to the synthesis of any desired complex carbohydrate structure.

The present case is analogous to the chemical synthesis of polynucleotides. In polynucleotide synthesis, methodology utilized for synthesis of short oligonucleotides can be readily utilized for generating longer or unnatural polynucleotide structures as well as polynucleotides having modified nucleic acids or mimetics or modified structures (e.g., the branched polynucleotides described in U.S. Pat. No. 5,710,264).

Although polynucleotides are inherently less complex than complex carbohydrates, they are synthesized using chemical synthesis methods which are inherently less efficient and less accurate than enzymatic processes. Thus, the methodology of the present invention, much like polynucleotide synthesis methods, can be applied with success to the generation of any complex carbohydrate structure.

Applicant would like to point out in this respect that claims of patents directed at polynucleotide libraries (see for example, U.S. Pat. No. 5,770,358 assigned to Affymax Technologies) are not limited by length or complexity of support-bound molecules. In such cases, as argued above, the synthesis of large combinatorial polynucleotide chains represents a practical impossibly, since the efficiency of such methodology tends to be inversely proportionate to the size of the polynucleotide chain thus limiting the length of the library constituents.

The present methodology, on the other hand, is far more efficient than chemical polynucleotides synthesis since enzymatic synthesis of complex carbohydrate structures is not radically effected by the size or complexity of the structure generated.

It is well known that enzymes which participate in the synthesis of complex carbohydrates are not effected by substrate size or complexity. For example, the preferred acceptors of human α-3/4-fucosyltransferase are Gal β 1,4 GlcNAc and Gal β1,3 GlcNAc. The acceptor specificity of this enzyme to carbohydrate structures of different sizes was characterized [Johnson et al. Glycoconjugate Journal (1992) 9:251-264]. As is shown in Table 2 of Johnson

et al., the relative activity of a purified α-3/4-fucosyltransferase is not effected by the size of the substrate; activity towards disaccharides was not radically different or higher than activity towards trisaccharides, tetrasaccharides or pentasaccharides.

In addition, it is also known that enzymes which participate in post translational modification of large globular proteins are not negatively effected by the size and/or complexity of the protein substrate and therefore are equally efficient in reactions using small or large protein substrates (see Table 5 of Johnson et al.).

Thus, enzymatic synthesis of complex carbohydrate structures is an accurate and an efficient approach to carbohydrate synthesis. In fact, enzymatic synthesis is far more efficient and accurate than widely used chemical synthesis techniques.

When synthesizing carbohydrates using chemical reactions, each addition of a carbohydrate unit to a pre-synthesized chain of carbohydrates involves several steps, mainly of protection, synthesis (unit addition) and deprotection. These steps call for use of harsh reaction conditions in terms of, for example, temperature, pressure, reagents concentration, acidity, etc., in order to achieve high reaction yield in each such step. It will be appreciated in this respect that the yield of each step has a major effect on the overall yield in multi-step chemical reactions. Thus, extreme conditions are pre-requisite for high step-yields. However, at present, such extreme conditions cannot be applied differentially to close locations on a solid support having a platform configuration. Hence, prior art practitioners turned to the use of a particulate (bead) type solid support or avoid the use of solid support altogether. Such particulates (or solutions) can be placed in dedicated sealed chambers of a conventional combinatorial chemistry apparatus, where the extreme conditions may selectively be applied. In order to reduce the total number of reactions employed, the traditional "split and pool" or "split and mix" combinatorial methodology was also applied by prior art

practitioners. Thus, prior art carbohydrate libraries are characterized by having individual members (structures) of the library attached to individual particulates or suspended in individual solutions. Individual particulates or solutions are then screened for activity (e.g., binding activity) and positive particulates or solutions are selected.

Since the "split and pool" methodology is also employed in library construction, the nature of the carbohydrate associated with each individual particulate of the library must be known. To this end, individual step labels are employed with particulates so as to allow to extract from a particulate of the library data pertaining to the synthesis steps in which it participated. Only then one theoretically knows which carbohydrate is attached to a specific particulate. However, since chemical reactions are typically of low yield (as compared to enzymatic reactions) and since a plurality of reactions are employed in the construction of any particular carbohydrate attached to any of the particulates of the library, in effect, the identity of the carbohydrate attached to the particulate cannot be determined with absolute certainty.

In sharp distinction to chemical synthesis, enzymatic synthesis is characterized by (i) high (close to 100 %) yield, as the enzymes lower the activation energy of the reactions; (ii) no need for multiple steps (protection, synthesis, deprotection) in order to execute the addition of a single carbohydrate unit to an existing carbohydrate chain; and (iii) no need for harsh reaction conditions.

An example describing a comparison between enzymatic synthesis and chemical synthesis of the same pentasaccharide is given by F. Yan et al. Polymer-supported and chemoenzymatic synthesis of *Neisseria meningitides* pentasaccharide: a methodological comparison. Carbohydrate research 328 (2000) 3-16. In this example a pentasaccharide was synthesized by 3 sequential enzymatic reactions with yields of > 95 % , > 95 % and > 99 % (scheme 4 in the paper), employing straight forward synthesis steps in mild physiological conditions without any protection and deportation, whereas the yields of the

equivalent chemical synthesis steps (performed non-enzymatically) were 45%, 66% and "not reported", whereby, each such chemical synthesis step involved many protection, deprotection and purification sub-steps.

As is described in the specification of the instant application, the complex carbohydrate library of the present invention represent naturally occurring complex carbohydrate structures, non-naturally occurring complex carbohydrate structures or a combination of both.

In the case of naturally occurring complex carbohydrate structures, it will be appreciated that given the state of the art at the day of filing the instant application and the detailed disclosure pertaining to enzymes which can be used by the present invention, it is the Applicant's strong opinion that it would be possible to synthesize in-vitro (on-support) any previously characterized naturally occurring carbohydrate structure since the present methodology is similar in many respects to in-vivo synthesis of naturally occurring carbohydrate structures. Thus, it is Applicant's strong opinion that a library including naturally occurring complex carbohydrate structures and portions thereof are enabled by the teachings of the present invention.

Complex carbohydrate structures that currently not found in nature (i.e., non-naturally occurring carbohydrates) can include slight or large modifications to naturally occurring complex carbohydrate structures or can be generated according to a predetermined design consideration. In any case, synthesis of non-naturally occurring complex carbohydrate structures is not more complicated than that of naturally occurring complex carbohydrate structures since such synthesis follows similar synthesis considerations. In fact, it is conceivable that in some cases, non-naturally occurring complex carbohydrate structures would be easier to generate than naturally occurring complex carbohydrate structures since non-naturally occurring complex carbohydrate structures can be designed while considering the types of enzymes and reactions needed. Thus, it is applicant's strong opinion that a library including non-naturally occurring carbohydrate structures is also enabled by the teachings of the present invention.

The Examiner further states that claim 30 encompasses complex carbohydrate libraries with carbohydrate members which contain unusual or unnatural sugars which may not be good substrates for the enzymatic synthesis reactions.

It will be appreciated that not all unusual or unnatural sugars are less efficient substrates for enzymatic reactions. In fact some modified or unnatural chemical derivatives of those sugars are better, more accessible substrates and as such are preferred in synthesis of complex carbohydrates. For example, The activity of the human enzyme β Gal-T1 towards GlcNAc is one order of magnitude lower then its activity towards p-Nitrophenyl-β- GlcNAc, a non-natural, chemical derivative of GlcNAc (See Table 1 of Amado et al. J.B.C. Vol. 273 No.21 pp. 12770-12778 1998). Results obtained by the present inventors following filing of the instant application further support the arguments presented above and clearly demonstrate that the methodology described in the instant application is highly suitable for parallel synthesis of addressable complex carbohydrate libraries on a single substrate. As is illustrated in Appendices A and B enclosed herewith, the present inventors have demonstrated the preparation of an addressable carbohydrate library on a single solid support.

Using mono di and tri saccharides having a terminal GlcNAc which is attached to a glass slide, and using the enzyme N-Acetyl-β-D-glucoseamine-β 1,4- galactosyltransferase which catalyzes the transfer of Galactose from UDP-Gal to a terminal GlcNAc and connecting it in a β1,4 glycosidic linkage, the present inventors were able to synthesize five <u>different carbohydrate structures,</u> each attached to a predefined location of a single glass slide (Appendix B).

In view of the above arguments and supporting data, Applicant believes to have overcome the 35 U.S.C. § 112, first paragraph, rejections.

35 U.S.C. § 112, Second Paragraph, Rejections

The Examiner has rejected claims 30-58 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiners rejections are respectfully traversed. Claim 30, 32, 34, 38, 40, 45, 52-55, and 57-58 have now been amended.

With respect to claim 30 the Examiner points out that the phrase "complex carbohydrate" is relative and undefined. Applicant would like to call the Examiners attention to the fact that the phrase "complex carbohydrate" is not only an art recognized term, which defines a polysaccharide (branched or not), i.e., a molecule which includes at least two covalently attached saccharide monomers, but it is also defined in both scientific literature and dictionaries. "Complex carbohydrates" is in fact the name of the first text book in the field of oligo- and poly- saccharides (Nathan Sharon, Addison Wesley Publishing company ,1975, ISBN 0-201-07324).

With respect to claim 34, the Examiner states that the term "harmless is indefinite and/or unclear. Claim 34 has now been amended to better define the conditions claimed.

With respect to claims 52-53 and 57, the Examiner states that the term "representation" is indefinite and/or unclear. Claims 52-53 and 57 have now been amended to better define the claimed subject matter.

In view of these amendments and remarks, Applicant believes to have overcome the 35 U.S.C. § 112, second paragraph, rejections.

35 U.S.C. § 103(a) Rejections

Dower et al. in view of Nicolaou et al and Schuster et al.

The Examiner has rejected claims 30-34, 36-40, 44-51 and 53-58 under 35 U.S.C. § 103(a) as being unpatentable over Dower et al. (U.S. Pat. No. 5,770,358) in view of Nicolaou et al. and further in view of Schuster et al. The

Examiner's rejections are respectfully traversed. Claim 30, 32, 34, 38, 40, 45, 52-55, and 57-58 have now been amended.

The Examiner points out that Dower et al. teach methods of synthesizing random oligomers including complex carbohydrates that utilize particle based synthesis methods. The Examiner further states that the library described by Dower et al. is addressable and includes linkers and that it would have been prima facia obvious to one of ordinary skill in the art to build the complex carbohydrate libraries taught by Dower et al. with the specific example of complex carbohydrate taught by Nicolaou et al. and the specific example of an enzyme used to link carbohydrates to a solid support described by Schuster et al.

As mentioned hereinabove, the present invention relates to methods of synthesizing <u>a single-support bound library of complex carbohydrates</u> in which each member of the library is bound at a specific and addressable location of a single support.

The teachings of Dower et al., Nicolaou et al. and Schuster et al. alone or in combination do not suggest or describe libraries which are bound to a single support since the fabrication of such libraries was neither conceived or enabled prior to the filing of the instant application.

The present inventors were the first to suggest and describe an addressable single support bound complex carbohydrate library.

The concept of a complex carbohydrate library which is bound to a single support in an addressable manner was formulated by the present inventors in response to a recognized need for complex carbohydrate libraries which can be screened in order to identify: (i) complex carbohydrate associated receptors or proteins as potential new carbohydrate related targets for drug therapy; (ii) complex carbohydrate associated receptors or proteins as potential new carbohydrate related targets for diagnostics; (iii) specific complex structural carbohydrate elements as potential new targets for drug therapy; (iv) the active sites of known complex carbohydrate structures; (v) new carbohydrate-based

biomarkers; and (vi) antibodies formed against carbohydrate-based epitope which is disease related.

Prior art carbohydrate libraries such as those described in the references cited by the Examiner cannot be efficiently utilized for all or some of the intended purposes described above. Prior art libraries were typically constructed for the sole purpose of finding carbohydrate ligands to specific molecules (e.g., lectin in Liang et al.), and as such, such libraries are less suitable for the intended purposes listed above since they are less suitable for high throughput screening of numerous proteins in efforts of identifying their carbohydrate ligands. Since the carbohydrate ligands are attached to addressable beads in prior art libraries, isolation of the protein bound bead can only be effected following chemical analysis of the bead bound tag.

In sharp contrast, the addressable single support library of the present invention is highly suitable for high throughput screening since a specific location on the support identifies the carbohydrate ligand and enables instant recognition of library members that react with a screened molecule.

The intended purpose of bead-bound prior art libraries clearly indicates a lack of need for high throughput large scale screening and as such a lack of need for complex carbohydrate libraries which are bound in an addressable manner to a single support. Clearly, the state of the art at the time of priority of the instant application suggests that screening of complex carbohydrate libraries was typically effected for the purpose of finding carbohydrate ligands to a known molecule, thus establishing multiple bead-bound carbohydrate libraries as the approach of choice and <u>clearly not providing an ordinary skilled artisan with any motivation</u> to seek new carbohydrate library configurations.

Thus, it is Applicant's strong opinion that one of ordinary skill in the art privileged to the teachings of Dower et al., Nicolaou et al. and Schuster et al. would not be motivated to produce the present invention, simply because the need for libraries constructed in the manner described by the instant application was not recognized.

As described hereinabove, complex carbohydrate libraries are traditionally prepared using combinatorial chemistry techniques. In order to create an addressable library using combinatorial chemistry techniques one needs to use beads as solid support and employ the split and pool methodology since as described hereinabove, combinatorial chemistry techniques cannot be applied to a single solid support to create the addressable complex carbohydrate library of the present invention.

The prior art does not mention or suggest enzymatic synthesis in order to construct an addressable library of carbohydrates that bound to a single solid support. All examples of enzymatic synthesis of prior art complex carbohydrates are limited to the synthesis of individual complex carbohydrate structures and not the synthesis of multiple complex carbohydrate bound to a single solid phase support in an addressable manner (i.e. an array type).

An enzymatically synthesized library attached to a single solid support having a flat platform configuration has advantages over a chemically synthesized library which is arranged on individual particulates, because (i) the carbohydrate structure present in each address (location) on the platform is known, and there is no need to label each address in accordance with the reaction steps it underwent, as is the case in chemical "split and pool" type synthesis; (ii) the carbohydrate structure present in each address (location) is far purer due to the far higher yields of enzymatic reactions as compared to chemical reactions (see related description hereinabove); and (iii) a single solid support configured as a microtiter plate can be used to simultaneously screen proteins against a plurality of glycan ligands.

The synthesis methodology outlined in the instant application was developed for the sole purpose of constructing the libraries of the present invention. Numerous synthesis parameters were considered while reducing the present methodology to practice. One of the most important parameters is what enzymes one should choose for synthesis of a specific carbohydrate and in what sequence to employ them, each enzyme has it range of acceptors and this should

be considered when selecting the enzymes and the order of using them for synthesis of specific structure. For example, see pages 41-42 of the filed application.

As is clearly demonstrated by Appendices A and B enclosed herewith, such methodology was used successfully by the present inventors to construct single support bound, addressable complex carbohydrate libraries which can be used for example, to screen molecules capable of specifically binding with various complex carbohydrate structures (exemplified in Appendix A).

Thus, it is Applicant's strong opinion that the teachings of the prior art cited by the Examiner would not motivate one of ordinary skill in the art to make the present invention nor would they provide a reasonable degree of success since the ordinary skilled artisan would recognize the inherent limitations of prior art methodology, which limitations would negate use in construction of the present invention.

The above arguments are strongly supported by the fact that prior to publication of the subject matter of the present invention, the present library configuration was neither mentioned nor suggested in the literature.

For example, Chi-Huey Wong a world-wide leading expert in the carbohydrate research field (having over 400 publications in the field), summarizes in a review published in February 2000 (Koeller and Wong Chem. Rev. Vol 100 pp. 4465-4493 2000) the developments in the field of carbohydrates synthesis. Chi-Huey Wong makes no mention of the concept underlying the present invention, i.e., a complex carbohydrate library which comprises a plurality of complex carbohydrate structures attached at specific and addressable locations to a single solid support. Thus, prior to the publication of the subject matter of the present invention, the concept of addressable complex carbohydrate libraries was not known.

However, following:

(i) a poster presentation and lectures given by Dr. Avinoam Dukler, a co-inventor of the present invention, at the Drug Discovery Technology Europe-

Conference held in Stuttgart Germany on April 24, 2001 (see, http://www.drugdisc.com/stuttgart/html/ddt-con1-main.asp) and Dr. Nir Dotan, a co-inventor of the present invention, at the biochemical society meeting in York UK on December 18, 2001 (see http://www.biochemistry.org/meetings/programme.cfm?meetno=675#1-1), and at IBC's Protein Microarray Technology meeting in Berlin on Sep 28, 2001 (see enclosed email-1);

(ii) a poster presentation and a lecture given by Dr. Ari Gargir an employee of Glycominds Ltd., the Assignee of the present invention, at IBC's Chips to Hit Microarray conference on October 28-Nov 1, 2001 (the poster won the best poster award, see enclosed email-2 and a copy of the award itself); and

(iii) a feature article entitled "The bittersweet promise of glycobiology" by Alan Dove published in Nature Biotechnology, vol. 19, pp 913-917 on October 2001, describing the inventors' invention of an array of complex carbohydrate for discovery of new carbohydrate binding proteins and as a basis for diagnostic tool to screen for antibodies against particular glycans; four papers published during 2002 expounded on the merits of addressable support-bound complex carbohydrate libraries and provided examples for fabricating such libraries [Wang et al. Nature Biotechnology Vol 20 pp. 275-281 March 2002; Houseman and Mrksich Chemistry and biology Vol 9. pp. 443-454 April 2002; Fukui et al. Nature Biotechnology 2002 Oct; 20(10):1011-7]; and Fazio F, Bryan MC, Blixt O, Paulson JC, Wong CH. Synthesis of sugar arrays in microtiter plate. J Am Chem Soc 2002 Dec 4;124(48):14397-402.

The importance and novelty of a combinatorial complex carbohydrate library which comprises a plurality of complex carbohydrate structures each attached at a specific and addressable site of a single solid support is further emphasized in the enclosed declaration by Prof. Nathan Sharon, a world-wide leading expert in carbohydrate research.

Thus, in view of the above arguments and the experimental support presented herein, it is Applicants strong opinion that the teachings of Dower et

al., Nicolaou et al. and Schuster et al. do not render obvious the claimed invention.

35 U.S.C. § 103(a) Rejections

Liang et al. in view of Seitz et al. and Seifert et al.

The Examiner has rejected claims 30-38, 44-51 and 53-58 under 35 U.S.C. § 103(a) as being unpatentable over by Liang et al. (Science 1996) in view of Seitz et al. (J. Am. Chem. Soc. 1997) and further in view of Seifert et al. (Tetrahedron Letters 1997). The Examiner's rejections are respectfully traversed. Claims 30, 32, 34, 38, 40, 45, 52-55, and 57-58 have now been amended.

The Examiner states that Liang et al. teach a carbohydrate library that contains approximately 1300 di- and trisaccharides which reads on claim 30. In addition the Examiner states that Liang et al. teach a library where individual members are attached to a solid support which reads on claim 30.

The Examiner further states that Seitz et al. teach enzymatic synthesis of large branched complex oligosaccharides on solid support and that Seifert et al. teach enzymes that can extend the length of a polymer bound oligosaccharide to create larger and more complex library members.

Thus, the Examiner concludes that it would have prima facia obvious to one having ordinary skill in the art at the time the invention was made to make the present invention.

As mentioned hereinabove, the present invention is of methodology for synthesizing a novel addressable <u>single-support</u> bound complex carbohydrate library.

This single support bound feature of the present invention, which is now a limitation of independent claim 30 is not rendered obvious by the teachings of Liang et al., Seitz et al. and Seifert et al. which clearly do not describe or suggest, alone or in combination, a single support bound addressable complex carbohydrate library.

Thus, it is Applicant's strong opinion that the present invention as embodied by now amended claim 30 is not rendered obvious by Liang et al. or in the alternative, by the combined teachings of Liang et al., Seitz et al. and Seifert et al.

In view of the above amendments and remarks it is respectfully submitted that claims 30-58 and 64 are now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

Sol Sheinbein
Attorney for Applicant
Registration No. 25,457

Date: January 19, 2003

Encl.:
Two months extension fee;
Response transmittal fee foe additional claims;
VERSION WITH MARKING TO SHOW CHANGES MADE
Information Disclosure Statement
A new Abstract of the invention on a separate sheet.
Appendix A
email-1
Award
email-2
Declarations (and attached CVs) by:
Dr. Nir Dotan
Prof. Nathan Sharon

The following publications:

WO02084249A2

US Patent No. 4,833,071

Mol Med Today 1999 Aug; 5(8):326-7

U.S. Pat. No. 5,770,358

Johnson et al. Glycoconjugate Journal (1992) 9:251-264

Crout and Vic. Glycosidases and glycosyl transferases in glycoside and oligosaccharide synthesis. Current Opinion in Chemical Biology. 1998, 2:98-111.

Koeller and Wong Chem. Rev. Vol 100 pp. 4465-4493 2000

"The bittersweet promise of glycobiology" by Alan Dove published in Nature Biotechnology, vol. 19, pp 913-917 on October 2001

Wang et al. Nature Biotechnology Vol 20 pp. 275-281 March 2002

Houseman and Mrksich Chemistry and biology Vol 9. pp. 443-454 April 2002;

Fukui et al. Nature Biotechnology 2002 Oct; 20(10):1011-7

F. Yan et al. Polymer-supported and chemoenzymatic synthesis of Neisseria meningitides pentasaccharide: a methodological comparison. Carbohydrate research 328 (2000) 3-16

Nathan Sharon, Addison Wesley Publishing company ,1975, ISBN 0-201-07324

Fazio F, Bryan MC, Blixt O, Paulson JC, Wong CH. Synthesis of sugar arrays in microtiter plate. J Am Chem Soc 2002 Dec 4;124(48):14397-402.

VERSION WITH MARKING TO SHOW CHANGES MADE

In the Specification:

Please replace the abstract filed with the application with the following:

Methods of synthesizing complex carbohydrate libraries having complex carbohydrate members which are bound in an addressable manner to a single support are provided.

In the Claims:

Claims 30, 32, 34, 38, 40, 45, 52-55, and 57-58 have now been amended, without prejudice, as follows:

30. (Amended) A method of producing an addressable ~~combinatorial~~ complex carbohydrate library, the method comprising the steps of:

(a) providing a single solid support having a plurality of addressable locations; and

(b) ~~enzymatically~~ synthesizing a plurality of complex carbohydrate structures, each of said plurality of complex carbohydrate structures being attached to at least one ~~addressed location~~ of said plurality of addressable locations, thereby producing the addressable ~~combinatorial~~ complex carbohydrate library.

32. (Amended) The method of claim 31, wherein said linker includes at least two ~~contiguous covalent bonds~~covalently linked monomers.

34. (Amended) The method of claim 33, wherein the linker is cleavable under conditions that do not affect a structure of each of said plurality of complex carbohydrate structures~~that are harmless to carbohydrates~~.

38. (Amended) The method of claim 30, wherein said single solid

support is ~~selected from the group consisting of addressable microparticles, addressable beads and~~ a flat platform.

40. (Amended) The method of claim 30, wherein said solid support is a chip and further wherein adjacent locations of said plurality of addressable locations are spaced no more than 2.25 mm from one another.

45. (Amended) The method of claim 30, wherein at least one of said plurality of complex carbohydrate structures includes at least two ~~contiguous~~ covalently linked saccharide units of a single species.

52. (Amended) The method of claim 30, wherein said plurality of complex carbohydrate structures ~~are a representation including~~ represent non-naturally occurring complex carbohydrates.

53. (Amended) The method of claim 30, wherein said plurality of complex carbohydrate structures ~~are a representation including~~represent naturally occurring ~~natural~~ complex carbohydrates.

54. (Amended) The method of claim 53, wherein said naturally occurring complex carbohydrates are associated with a condition selected from the group consisting of tumorogenesis, metastasis, pregnancy, vascular disease, heart disease, neurodegenerative disease, autoimmune disease, infertility, allergies, embriogenesis, apoptosis, neurodegenerative disorders and organ transplantation.

55. (Amended) The method of claim 53, wherein said naturally occurring complex carbohydrates are ~~derived from a~~present in human ~~source~~cells.

57. (Amended) The method of claim 30, wherein said plurality of

complex carbohydrate structures ~~are a representation of~~represent domains of at least one naturally occurring complex carbohydrate.

58. (Amended) The method of claim 57, wherein said at least one naturally occurring complex carbohydrate is present in~~derived from a~~ human ~~source~~ cells.

Please add New claim 64 as follows:

64. (New) The method of claim 30, wherein step (b) is effected by on-support, parallel enzymatic synthesis of said plurality of complex carbohydrate structures.